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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,634	11/25/1997	ELAZAR RABBANI	ENZ-53(DIV-2	4640

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EXAMINER	
SHIN, DANA H	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
05/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,634	RABBANI ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007 and 02 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *275,289,290 and 296-301* is/are pending in the application.

4a) Of the above claim(s) *289,290 and 298-301* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *275,296 and 297* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-11-08, 1-14-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on December 3, 2007 and March 2, 2008.

Currently, claims 275, 289-290, and 296-301 are pending, and claims 275 and 296-297 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Election/Restrictions

Applicant's election with traverse of claims 275 and 296-297 in the reply filed on March 2, 2008 is acknowledged. The traversal is on the ground(s) that the inventions of groups I-III have a common functionality, although the effects of the inventions are different. This is not found persuasive because the claims are distinct if the inventions have a materially different

design, mode of operation, function, or effect. Since the inventions have different effects as acknowledged by applicant, the inventions of groups I-III are distinct. Further, applicant argues that there is no search burden to search all inventive groups. Contrary to applicant's argument, the inventions require a different field of search, for example employing different search queries, and therefore the prior art applicable to one invention would not likely be applicable to another invention, thereby imposing a serious search burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Response to Arguments

Applicant's arguments with respect to claims 275, 283, and 295 have been considered but are not persuasive because applicant's arguments pertain to the newly amended claims. Furthermore, claims 283 and 295 are now cancelled. See below for new grounds of rejections necessitated by amendment.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 297 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a multimeric complex composition of multiple monomeric units of insulin that are covalently attached to one another.

Throughout the entire disclosure of the specification, there is only one occurrence where a single "potential" utility for the claimed multimeric complex of insulin is indicated such that it "could be useful in that manner in diabetic treatment". See page 78. In addition, the specification is devoid of any working example demonstrating that the claimed composition of claim 297 is indeed useful in diabetic treatment. Contrary to the prophetic teaching that the claimed multimeric complex of insulin is useful for diabetic treatment, covalent insulin dimers were specifically warned against being used in diabetic treatment at the time of the invention. For example, Ekwuribe (US 5,438,040) teaches that insulin has been used as a therapeutic drug for diabetes since 1922. See column 4, lines 4-13. Ekwuribe teaches that "There is significant evidence that the incidence of immunological responses to insulin may result from the presence of covalent aggregation of insulin in blood of insulin-using diabetic patients." See column 5, lines 44-49. In addition, Ekwuribe teaches that as many as 30% of diabetic subjects receiving insulin show specific antibodies to "covalent insulin dimers" and therefore it is recommended that the covalent insulin dimer content is maintained below 1%. See column 5, lines 57-66.

Given the specific teachings against increasing covalent insulin dimer content and the art-recognized recommendation for making insulin products that are low in the covalent insulin dimer content for diabetes treatment, the instantly claimed multimeric insulin composition is considered to lack the asserted utility as a diabetes therapeutic composition. Since the prior art

reference of Ekwuribe taught away from the claimed composition, in particular with regard to the single asserted therapeutic utility in a diabetes treatment regimen, a person skilled in the art would not have been able to make the claimed multimeric composition of insulin and use it in a diabetes treatment method as suggested by the specification. Furthermore, the specification does not disclose any factual evidence that the claimed multimeric composition of insulin could work as a diabetes treatment drug as asserted in the specification.

Since the specification fails to adequately describe how to use the invention as a diabetic therapeutic composition as stated in the specification, despite the art-recognized counsel against the use of covalent insulin dimers, it is concluded that the claimed invention for diabetes treatment is not enabled at the time of the invention and that one of ordinary skill in the art would not have made and used the claimed composition without undue experimentation at the time of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

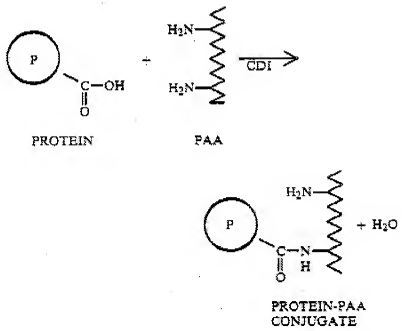
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 275 and 296-297 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ryser et al. (US 4,847,240) in view of Wu et al. (US 5,166,320).

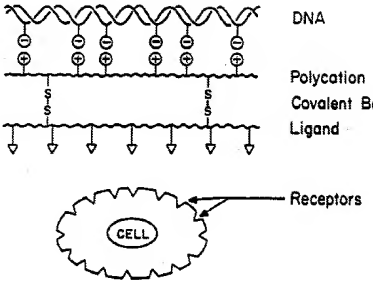
The claims are drawn to a multimeric complex composition of multiple monomeric units of protein that is a ligand to a cell surface receptor, wherein the monomeric units are covalently attached to one another via a polynucleotide and a binding matrix-forming polynucleotide, wherein the ligand to a cell surface receptor is a hormone, wherein the hormone is insulin.

Ryser et al. teach that a protein molecule (e.g., protein hormones) or a macromolecule (e.g., cancer drug methotrexate) can be covalently bound to polymers such as a poly amino acid (PAA) in soluble form, thereby forming a supramolecular structure. They teach that the PAA-conjugated proteins or macromolecules confer enhanced cellular uptake and therefore can be efficiently transported into cells without losing the biological activity of the protein molecules (hormones) or the macromolecules (cancer drug methotrexate), wherein the supramolecular structure is illustrated in column 8 and replicated below:



Ryser et al. specifically teach that the supramolecular composition is "useful in enhancing the cellular uptake of protein hormones or polypeptide hormones, such as insulin, especially when specific receptors for such hormones have been abolished or damaged by mutations or by diseases." See column 16, lines 27-31. Ryser et al. do not teach that the polymer that covalently conjugates the protein hormones such as insulin is a polynucleotide instead of a poly amino acid sequence.

Wu et al. teach a polynucleotide carrier system comprising a molecular complex of a ligand for a protein receptor that complexes the polynucleotide , wherein the carrier system is soluble in a physiological fluid, as illustrated in Figure 1, which is replicated below:



It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the supramolecular composition structure of Ryser et al. by replacing the covalently-binding poly amino acid (PAA) with the colvalently-binding polynucleotide of Wu et al., thereby producing a multi-complex of hormones covalently linked via polynucleotides.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success, because Ryser et al. taught that protein hormones or polypeptide hormones, such as insulin, can be more efficiently delivered into target cells when the protein hormones are covalently bound to polymers such as a poly amino acid (PAA) in soluble form, thereby forming a supramolecular structure, and because Wu et al. taught the carrier system structure comprising a polynucleotide (a polymer) that is covalently attached to a ligand for a protein receptor for delivering the polynucleotide into target cells. Since the use of polymers for covalently conjugating or attaching to protein hormones or ligands for protein receptors with a resultant effect of enhanced cellular uptake of the protein hormones was known in the art, one of ordinary skill in the art trying to increase the efficiency of cellular uptake of protein hormones or

ligands for protein receptors would have been motivated to conjugate them to a polymer such as a polynucleotide or a poly amino acid, which covalently binds to the protein/ligand molecules. Further, one of ordinary skill in the art desiring to deliver more than one unit of protein hormone or ligand in a simultaneous manner would have been motivated to covalently attach each protein/ligand to make a multimeric compound comprising multiple units of protein hormones or ligands, by utilizing the inherent property of polynucleotides that hybridize with complementary nucleotide sequences as depicted by Wu et al. Since the utility of polymers as carriers for hormones (e.g., insulin) was known in the art as taught by Ryser et al., and since the polynucleotide carrier system structure comprising a ligand for a protein receptor linked to a polynucleotide was known in the art as taught by Wu et al., one of ordinary skill in the art would have had reasonably arrived at the claimed multimeric composition at the time of the invention. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

This application contains claims 289-290 and 298-301 drawn to inventions nonelected with traverse in the reply filed on March 2, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635